WNT-activated bone grafts repair osteonecrotic lesions in aged animals.

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Public Summary:
The Wnt pathway is a new target in bone therapeutic space. WNT proteins are potent stem cell activators and pro-osteogenic agents. Here, we gained insights into the molecular and cellular mechanisms responsible for liposome-reconstituted recombinant human WNT3A protein (L-WNT3A) efficacy to treat osteonecrotic defects. Skeletal injuries were coupled with cryoablation to create non-healing osteonecrotic defects in the diaphysis of the murine long bones. To replicate clinical therapy, osteonecrotic defects were treated with autologous bone graft, which were simulated by using bone graft material from syngeneic ACTB-eGFP-expressing mice. Control osteonecrotic defects received autografts alone; test sites received autografts treated ex vivo with L-WNT3A. In vivo microCT monitored healing over time and immunohistochemistry were used to track the fate of donor cells and assess their capacity to repair osteonecrotic defects according to age and WNT activation status. Collectively, analyses demonstrated that cells from the autograft directly contributed to repair of an osteonecrotic lesion, but this contribution diminished as the age of the donor increased. Pre-treating autografts from aged animals with L-WNT3A restored osteogenic capacity to autografts back to levels observed in autografts from young animals. A WNT therapeutic approach may therefore have utility in the treatment of osteonecrosis, especially in aged patients.

Scientific Abstract:
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